Outcomes in children treated for tuberculosis with the new dispersible fixed-dose combinations in Port Moresby

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ABSTRACT

Setting: The new child-friendly fixed dose combinations (FDCs) were introduced at Port Moresby General Hospital, Papua New Guinea, in 2016 for the first-line treatment of children (<15 years) with tuberculosis (TB) who were less than 25 kilograms.

Objective: To describe the characteristics and outcomes for children treated with the new FDCs, and to identify risk factors for unfavorable treatment outcomes.

Design: A retrospective cohort study of all children treated for TB with the FDCs from August 2016 to August 2017.

Results: 713 children were included, and 488 (68%) were diagnosed as pulmonary TB. Only 6 (0.8%) TB cases were bacteriologically confirmed and HIV status was known in 50%. Treatment outcomes were favorable in 425 (60%) children. **Of 288 with unfavorable outcomes, 242 (84%) were loss to follow-up (LTFU) and 25 (8.4%) were known to have died.** Children who were severely underweight (<-3 weight-for-age Z score) on presentation were at greater risk of LTFU compared to children of normal weight on multivariable analysis (aRR 1.3, 95% CI 1.0-1.6, p<0.05).

Conclusion: **Alternative** models of care to reduce LTFU during treatment need consideration, including integration with nutritional support. **Improving diagnosis through microbiological confirmation of TB and HIV are major challenges to be addressed.**

INTRODUCTION

Tuberculosis (TB) is a major cause of morbidity and mortality among children in high burden countries.[1] Globally in children (<15 years of age) in 2016, there were an estimated 1.04 million incident cases of TB and 253,000 TB related deaths.[2] In Papua New Guinea (PNG) in 2016, the case notification rate for all forms of TB was 333 per 100,000 population and children accounted for 27% of all TB case notifications,[3] higher than the global estimate of 10.6% of all TB cases **and the highest proportion of TB cases in children reported globally**.[2] The vast majority of child TB cases in PNG are clinically diagnosed without bacteriological confirmation.

The burden of TB is high in the National Capital District (NCD) in 2016, with a case notification rate of 1,117 per 100,000 population, of which 21% occurred in children.[3] In 2016, 42.5% of TB cases in the NCD were tested for HIV, compared to the national average of 35%, and 7.6% of those tested in NCD were HIV-positive.[3] Treatment success has remained low throughout the country, ranging from 55% to 65% during 2008 to 2016, **and lost to follow-up (LTFU) is common**.[3]

Young age is a consistent risk factor for mortality in children with TB. An estimated 80% of all child TB deaths globally in 2015 occurred in children under 5 years of age.[4,5] Young children require higher dosages per weight than older children and adults to achieve adequate **drug exposure**. Hence, the World Health Organization (WHO) increased the recommended dosages for the first-line drugs to treat TB in young children in 2010.[6] Further, the previously available formulations were difficult to administer to young children to achieve these dosages, often requiring breaking multiple tablets into portions with concerns about accuracy of dosing.[7] These challenges led to the development of appropriately-dosed, child-friendly, dispersible fixed-dose combinations (FDCs) consisting of RHZ (75 mg/50mg/150mg) and RH (75mg/50mg) for the treatment of drug-susceptible (DS) TB in children weighing less than 25 kg; these FDCs were launched in December 2015.[6,8]

PNG was the first country in the Asia-Pacific region to introduce the new FDCs at Port Moresby General Hospital (PMGH) situated in the NCD in August 2016. We aimed to describe the characteristics and treatment outcomes for children treated with

the new FDCs at PMGH and to identify risk factors associated with unfavorable outcomes.

METHODS

Study Setting

Port Moresby is the capital of PNG with a population of 365,000. PMGH is the largest hospital in PNG with 1000 beds, including 138 paediatric beds, that provides care for child TB cases, mainly from the NCD and Central Province. Children treated for TB at PMGH may present as inpatients or outpatients. The approach to the diagnosis of pulmonary TB in children includes clinical evaluation, TB contact history and chest radiography. Expectorated sputum is collected if available, otherwise gastric aspirates are obtained if directed by the clinician. Two sputum samples are sent to the laboratory for examination by smear microscopy for acid-fast bacilli and Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA). Only specimens in which rifampicin resistance is detected by Xpert are sent to Queensland Mycobacterium Reference Laboratory in Australia for mycobacterial culture and drug susceptibility testing. Laboratory investigation of extra-pulmonary TB is dependent on the site of disease, such as fine needle aspiration of lymph nodes or examination of cerebrospinal fluid. **Routine** HIV testing is encouraged, but **not always performed due to: lack trained staff (certified training is required); patient volume; and properly recording data.**

Study Design and Population

This was a retrospective cohort study of all children (<15 years) with presumptive DS-TB who were treated with the new FDC from the commencement of TB treatment at PMGH over a one-year period (17th August 2016 to 16th August 2017).

Management of TB in Children

Treatment regimens for TB were in accordance with national guidelines.[9,10] First-line treatment included a two-month intensive phase of daily rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) followed by a continuation phase of four months of daily rifampicin and isoniazid (2RHZE/4RH) for children with pulmonary

TB. All forms of extra-pulmonary TB were treated for nine months with a continuation phase of seven months (2RHZE/7RH). Corticosteroids are routinely given for 6 weeks in children with TB meningitis or pericardial TB.

Weight-based dosing of the FDCs was used as described in Table I as per national guidelines.[9,10] Following hospital discharge for inpatients or treatment initiation for outpatients, children were provided with treatment for two weeks and requested to attend the PMGH outpatient TB clinic for follow-up. Children severely underweight (weight-for-age Z score <-3) on hospital admission were requested to attend the nutritional rehabilitation clinic two weeks after discharge until they reached their target weight, and were followed up at the outpatient child TB clinic.

In PNG, children receiving treatment for drug-susceptible TB are supervised by family members, with no formal directly-observed treatment. Families were educated about TB treatment by the provider, and given incentives as described below when available. Children are followed every 1-2 months with medication provided until the next scheduled clinic visit. At each follow-up visit, children completed evaluation which included weight, clinical history to determine resolution or persistence of symptoms, assessment of adherence to and **tolerance of medication**. The numbers of dispersible FDC tablets to be taken each day was adjusted according to the current weight (Table 1); if a child weighed ≥25 kilograms, they were changed to "adult" preparations of FDC as per guidelines.[9,10] Repeat sputum or gastric lavage was not done in children who had been diagnosed with bacteriologically confirmed TB. Incentives were provided when available, which included monthly transport vouchers (~$2.80 USD) and shopping vouchers (~$14 USD) at the end of the intensive phase and upon treatment completion. In addition, they received a gift pack of books and pencils on treatment completion.

Data collection and analysis

Data variables collected in this study included: residence, age, sex, weight, weight for age, site of TB, type of TB, HIV status and treatment outcomes which were reported according to standard WHO and national definitions.[9,11] Data were captured in 'E TB Manager' tablets that were introduced to PMGH together with the introduction of the new FDC in August 2016 by Rural Sensing Centre and the National Health

Information System in PNG. After data capture, data describing children treated for DS-TB were downloaded into an electronic database and then made available in Microsoft Excel (Microsoft, Redmond, Washington, USA). Data were cross-checked with treatment registers, follow-up clinic registers, and paediatric admission and inpatient death register books.

Data were validated and analysed in Stata v15 (StataCorp, College Station, Texas, United States). Categorical data were reported as numbers and proportions. Continuous data were reported as median and inter-quartile range. A modified Poisson regression using robust variance estimates was used for analysis of risk factors. Associations were summarised and inferred using relative risk (RR, unadjusted and adjusted) and 95% confidence intervals (CIs).

Ethics

Ethical approval to conduct this study was obtained from the PNG Medical Research Advisory Council, The Port Moresby General Hospital, and the Alfred Hospital Ethics Committee, Australia. As this study involved routinely collected, secondary programme data, waiver of informed consent was sought and approved by the ethics committees.

RESULTS

There were 713 children who initiated treatment with the new FDCs over a one-year period. Demographic and clinical characteristics are summarized in Table 2, and 554 (78%) children were recorded as being resident in the NCD. The majority (77%) of the children were < 5 years of age, reflecting the fact that the new FDCs are only for children weighing less than 25 kilograms (Table I), and 117 (16%) of the study population were infants (<12 months of age). Pulmonary TB (68% of total cases) was the most common site and extra-pulmonary TB included: lymph node TB (9% of total cases), TB meningitis (7%), abdominal TB (4%), and pleural TB (2%). Less than 1% of the cohort had bacteriologically confirmed TB. HIV status was unknown in 50% of the cohort, and among 357 children with known HIV status, 13% were living with HIV.

Table 3 presents data on treatment outcomes. There were no children recorded as "cured" as sputum was not collected for microscopy or culture at follow-up. There were 25 deaths. The median time from starting treatment until death was 10 days, though with a wide range (IQR 6, 53; n=21). Of children who died, 15 (60%) had PTB and 7 (28%) had disseminated disease, 5 with TB meningitis and 2 with miliary TB. Seven (28%) of the deaths were in children newly diagnosed with HIV, and 9 (36%) were HIV-negative or unknown.

One-third (34%) of all children in the cohort were LTFU. Characteristics associated with the outcomes of "treatment complete" (n=425) and "LTFU" (242) were assessed (Table IV). Children who were severely underweight (<-3 weight-for-age Z score) on presentation were at significantly greater risk of LTFU compared to children of normal weight on multivariable analysis adjusting for potential confounders (adjusted RR 1.3, 95%CI 1.0-1.6, p<0.05). Multivariable analysis similarly adjusted for potential confounders did not identify any factors associated with unfavorable outcomes defined collectively as died, LTFU, and not evaluated (data not shown). However, **93 (44%) of 212 severely underweight children (WFA Z score of <-3) were not tested for HIV.**

DISCUSSION

This is a cohort study reporting outcomes in children treated with the recently developed FDCs for DS-TB. Our findings highlight the challenges of TB confirmation and retention in care that are common in many resource poor settings. The mortality rate of 3.5% found in our study is higher than the 2% previously reported from a cohort study of 639 children who received first-line treatment for pulmonary and extra-pulmonary TB as single drug preparations in the 1980s at PMGH.[12] In comparing outcomes of these two large PNG child TB cohorts it should be noted that the previous study was conducted in the pre-HIV era and included older children while our study was limited to children weighing less than 25 kilograms. Young age and HIV are recognized risk factors for mortality in children treated for TB.[4] While child TB is commonly diagnosed and reported in PNG,[3] treatment outcomes, including TB-related deaths are not well reported. Deaths due to severe TB in children can be under-represented in surveillance data because they often occur early following presentation and diagnosis before the child can be registered as a TB

case.[13] Most of the recorded deaths occurred as inpatients within weeks following diagnosis. There is a recognized need for better data of TB-related deaths in children.[1,4,5] This study also highlights the need to improve coverage of testing for HIV in children with presumptive TB.

The high proportion of children LTFU described here is similar to a previous study from PMGH[12] , where the LTFU rate was 28%. Both studies may underestimated the true mortality rate as there were likely to have been deaths among the children who were LTFU. LTFU is recognized to be a major contributor to the low treatment success rates that were recently reported for PNG – representing around 19% of all treatment outcomes in 2016 but as high as 27% in some settings.[3] LTFU and poor treatment adherence are frequent in cohorts of children treated for TB in high-burden settings.[14,15] One of the commonly perceived treatment barriers to adherence, a lack of child-friendly medicines, was not a factor in this cohort and yet retention in care remained a challenge. LFTU also occurred despite the use of incentives. However, incentives were provided inconsistently during this study period which highlights the challenges of access and follow-up when care is centralised in a large tertiary facility. Of note, the LTFU rate may have been lower than reported, as TB clinic staff may have failed to record clinic attendance in the register and accurately document treatment outcomes. Improving the quality of TB program data is an important to ensure that the data can be meaningfully used to inform accurate reporting and quality improvement activities.

Children who were severely undernourished were at highest risk of LTFU. However, when adjusting for measured potential explanatory factors, the effect size was not large, suggesting that other unmeasured factors exist. There is a known higher risk of death among children with severe malnutrition which could explain the higher rate of LTFU. Additionally, it is possible that these children chose to attend nutritional rehabilitation services for follow-up suggesting that coordination with nutritional services may support retention in the TB cascade of care. **Finally, HIV status was unknown in a large proportion of the cohort including children with severe malnutrition, and undiagnosed HIV-infected children not being treated with antiretroviral therapy are at risk for severe malnutrition and poor outcomes. Having enough trained staff to perform HIV testing in the hospital and clinic was challenging, in addition to capturing HIV testing into the electronic tablet.**

This is the first study of outcomes of children receiving FDCs in our population and will serve as a benchmark to measure future efforts to improve care. Factors associated with LTFU are likely to be multiple and complex including behavioral, socioeconomic and healthcare system related. Improving retention in care will require consideration of these factors when treating paediatric TB. Enabling patients to receive care closer to home by enhancing community-based treatment support may be an important factor to promote.[15]

The proportion of all TB in PNG that is bacteriologically confirmed is low (26% of pulmonary TB cases) and the diagnosis of pulmonary TB without sputum or of extra-pulmonary TB is common.[3] Low rate of bacteriological confirmation (less than 1%) underlines the challenges of TB diagnosis in children. Additionally **for this study,** accurately recording specimen collections into the electronic tablet was challenging. **The consistently low diagnostic yield from smear microscopy of gastric aspirates and lack of culture facilities has discouraged clinicians in PNG from routinely taking specimens for bacteriological confirmation of TB in children.** The WHO and PNG guidelines now recommend that children with presumptive TB have specimens tested using GeneXpert[9,11] **and mycobacterial culture is also now available (since 2017) in Port Moresby.** Optimising the use of **Xpert, culture and drug susceptibility** testing to improve the diagnosis of child TB is important, especially in PNG that has an increasingly high burden of drug-resistant TB.[16] Obtaining specimens from young children remains a challenge, **especially in a setting where nasogastric tubes are often not available**. **Nonetheless, efforts to improve the laboratory detection of *Mycobacterium tuberculosis* and the spectrum of drug resistance in children are required.**

This study has a number of important limitations. We did not have a control group that would allow a comparison to be made between treatment outcomes achieved using the new FDC formulations compared to the former. Additionally, this was a retrospective study reliant on routinely collected programmatic data. As such there were missing data that despite cross checking registers, were not able to be identified, especially in regards to specimen collections for GeneXpert and HIV. While this study aimed to determine risk factors for LTFU, the results may not be a true reflection of actual risk factors as key information, notably HIV status, was missing for a large proportion of patients. Additionally, some children may have had

undiagnosed drug resistant TB. Finally, we were unable to actively trace the large proportion of the cohort who were LTFU to determine their status and ascertain the possible reasons for not completing TB treatment at PMGH.

In conclusion, this study of a large cohort of children treated with the new FDC in PNG highlighted the need to improve retention in care, promote bacteriological confirmation of TB among children, increase access to HIV testing and improve linkages with community-based TB programs and nutrition services.

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Conflict of interest

There are no conflicts of interest to declare**.**

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Author contributions

The Child TB Project was developed by TI, JA, AM and HW. VA, SG, AM, HDS, ML and HW contributed to the drafting of the study proposal. VA, ML sought and received ethical clearance. The project was managed by GS, VA, ML, JA, HW, and TM. VA, SG, PC, HDS contributed to data analysis. VA, ML, SG, AM, PC, HDS drafted the final manuscript and all authors reviewed and contributed to it.

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Table 1. Dosing regimen by weight bands for the treatment of tuberculosis in children using the new dispersible fixed-dose combinations at Port Moresby General Hospital, Papua New Guinea [8,9]

Weight bands	Numbers of tablets		
	Intensive phase		Continuation phase
	RHZ* 75/50/150 mgs (Dispersible tablets)	Ethambutol 100 mg	RH*75/50 mgs (Dispersible tablets)
4 – 7.9 kg	1	1	1
8 – 11.9 kg	2	2	2
12 – 15.9 kg	3	3	3
16 – 24.9 kg	4	4	4
≥ 25 kg	Go to adult dosages and preparations		

*R, Rifampicin; H, Isoniazid; Z, Pyrazinamide

Table 2. Clinical and demographic characteristics of children who commenced treatment of tuberculosis using the new dispersible fixed-dose combinations at Port Moresby General Hospital, Papua New Guinea from August 2016 to August 2017

Characteristic	Number (%)
Total	**713**
Age	
<12 months	117 (16.4)
12-59 months	431 (60.4)
60-119 months	141 (19.8)
≥120 months	23 (3.2)
Missing	1 (0.1)
Gender	
Male	387 (54.3)
Female	325 (45.6)
Missing	1 (0.1)
Residence	
National Capital District	554 (77.7)
Central province	144 (20.2)
Gulf province	4 (0.5)
Others	2 (0.3)
Missing	9 (1.3)
HIV status	
Uninfected	308 (43.2)
Infected	49 (6. 9)
Not known	356 (49.9)
Baseline weight	
< 4 kg	4 (0.5)
4-7.9 kg	216 (30.3)

8-11.9 kg	229 (32.1)
12-15.9 kg	135 (19.0)
16-24.9 kg	119 (16.7)
Missing	10 (1.4)
Site of TB	
Pulmonary TB (PTB)	488 (68.4)
TB Lymph node	66 (9.3)
TB Meningitis	47 (6.6)
Extra-pulmonary TB (EPTB) - Others	108 (15.1)
Missing	4 (0.6)
Case Definition	
PTB bacteriologically confirmed	1 (0.1)
PTB clinically diagnosed, bacteriologically negative	34 (4.8)
PTB clinically diagnosed, not tested bacteriologically	427 (59.9)
EPTB bacteriologically confirmed	5 (0.7)
EPTB clinically diagnosed	230 (32.3)
Case definition not recorded	16 (2.2)

Table 3. Treatment outcomes of children who commenced treatment of tuberculosis using the new dispersible fixed-dose combinations at Port Moresby General Hospital, Papua New Guinea

End of treatment outcomes	Number (%)
Total	**713 (100)**
Cured	0 (0)
Treatment completed	425 (59.6)
Treatment failed	0 (0)
Died	25 (3.5)
Lost to follow-up	242 (33.9)
Not evaluated*	21 (3.0)
Not recorded	0 (0)

*** Not evaluated is defined as: a TB patient for whom no treatment outcome is assigned. This includes cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.**

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395 **Table 4. Risk factors for lost to follow-up as compared to treatment success in**
396 **children treated with the new fixed-dose combinations at Port Moresby General**
397 **Hospital**

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Characteristic	Treatment Complete N (%)	Lost to follow-up N (%)	RR (0.95 CI)	aRR** (0.95 CI)
Total	**425 (63.7)**	**242 (36.3%)**	**-**	**-**
Age in months (n=667)				
<12	58 (13.6%)	44 (18.2%)	1.05 (0.6, 1.8)	1.2 (0.7, 2.2)
12-59	258 (60.7%)	151 (62.4%)	0.9 (0.5, 1.5)	1.1 (0.6, 1.8)
60-119	96 (22.6%)	38 (15.7%)	0.7 (0.4, 1.2)	0.8 (0.5, 1.5)
≥120	13 (3.1%)	9 (3.7%)	Ref	Ref
Gender (n=667)				
Male	233 (54.8%)	134 (55.4%)	Ref	Ref
Female	192 (45.2%)	108 (44.6%)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
Residence (n=662)				
National capital district	339 (80.3%)	181 (75.4%)	Ref	Ref
Central province	80 (19.0%)	56 (23.3%)	1.2 (0.9, 1.5)	1.1 (0.9, 1.4)
Others	3 (0.7%)	3 (1.3%)	1.4 (0.6, 3.2)	1.6 (0.6, 2.6)
HIV status (n=667)				
Uninfected	187 (44.0%)	105 (43.4%)	Ref	Ref
Infected	26 (6.1%)	14 (5.8%)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)
Unknown	212 (49.9%)	123 (50.8%)	1.0 (0.8, 1.3)	1.1 (0.9, 1.3)
Type of patient (n=665)				
New	402 (94.8%)	232 (96.3%)	Ref	Ref
Previously treated	22 (5.2%)	9 (3.7%)	0.8 (0.4, 1.4)	0.8 (0.4, 1.4)
Site of TB (n=666)				
Pulmonary TB	288 (67.8%)	171 (71.0%)	Ref	Ref

TB Lymph Node	42 (9.9%)	20 (8.3%)	0.9 (0.6, 1.3)	1.4 (0.6, 2.9)
TB Meningitis	24 (5.6%)	17 (7.1%)	1.1 (0.8, 1.6)	1.6 (0.8, 3.5)
Extra-pulmonary TB-Others	71 (16.7%)	33 (13.7%)	0.98 (0.6, 1.2)	1.3 (0.6, 2.6)
Case Definition (n=666)				
Bacteriologically confirmed	4 (0.9%)	2 (0.8%)	0.9 (0.3, 2.7)	0.8 (0.2, 2.7)
PTB clinically diagnosed	275 (64.7%)	167 (69.3%)	Ref	Ref
EPTB clinically diagnosed	146 (34.4%)	72 (29.9%)	0.9 (0.7, 1.1)	0.8 (0.4, 1.4)
Baseline weight for age Z score (n=658)				
Normal (≥-2 Z score)	203 (48.2%)	99 (41.8%)	Ref	Ref
Underweight (<-2 to -3)	97 (23.0%)	47 (19.8%)	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)
Severe underweight (<-3)	121 (28.7%)	91 (38.4%)	1.3 (1.1,1.6) *	1.3 (1.0, 1.6) *

-; *p<0.05; ** Modified Poisson regression using robust variance estimates

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